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September 2, 1999



PATENT APPLICATION  
Attorney's Docket No.: DUK96-03pA3

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#23  
PLUNKET  
9/10/99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jonathan S. Stamler and Andrew J. Gow  
Application No.: 08/796,164 Group: 1654  
Filed: February 6, 1997 Examiner: B. Celsa  
For: Modified Hemoglobins, Including Nitrosylhemoglobins,  
And Uses Therefor

CERTIFICATE OF MAILING	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231	
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INTERVIEW SUMMARY

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

On August 5, 1999, an interview was conducted at the United States Patent and Trademark Office. Carol A. Egner and David E. Brook (Attorneys of Record) and Jonathan S. Stamler, M.D. (Applicant) discussed the application with Bennett Celsa (Patent Examiner).

Example 19 of the Stamler *et al.* patent application WO 93/09806 (also appearing as Example 4 of US 5,380,758 and Example 19 of US 5,593,876) was discussed as it affects the claims of the subject application. Related applications 08/616,371 filed March 15, 1996, 08/667,003 filed June 20, 1996, and 08/874,992 filed June 12, 1997 were also discussed during the same interview.

WO 93/09806 was the subject of a Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 ("Declaration of Dr. Stamler") mailed to the United States Patent and Trademark Office on January 6, 1999 for the subject application. At the interview, it was explained to Mr. Celsa that Example 19 of WO 93/09806 and Example 1 of U.S. Patent Application No. 08/559,172 (abandoned as of July 6, 1999), both purporting to show synthesis of

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SNO-hemoglobin, both arose from the same set of experiments performed by Dr. Stamler, even though the accounts of those experiments in the Examples differed in details of the procedure, and both were, in fact, inaccurate in some aspects.

Dr. Stamler elaborated on the statements presented in his Declaration of January 6, 1999. He explained that the experiment resulting in the spectrum of Figure 28 of WO 93/09806 and Figure 1 of 08/559,172 employed acidified nitrite as the reagent. Although the assay to detect SNO-hemoglobin had been done incorrectly, even had the assay been performed correctly, the products were dissociated hemes and dissociated, denatured subunits. Similar treatment of more acid resistant proteins had resulted in the production of *S*-nitrosoproteins. Figure 29 of WO 93/09806 (Figure 2 of 08/559,172) shows the result of an experiment in which *S*-nitroso-N-acetylcysteine (SNOAc) was added to hemoglobin. Although the description in the Examples refers to a different conclusion, the correct conclusion apparent to one of skill in the art is that the spectrum shows that the product contains oxidized hemoglobin, methemoglobin.

As was explained in item 5 of the Declaration of Dr. Stamler, the experimental conditions one might conclude from the Examples were used in an attempt to synthesize SNO-hemoglobin, were tried in more recent experiments in Dr. Stamler's laboratory. Using 12.5  $\mu$ M SNOAc and 12.5  $\mu$ M hemoglobin at pH 6.9 did not produce detectable SNO-hemoglobin. See Exhibits E1-E3 with the Declaration of Dr. Stamler.

In future prosecution, Mr. Celsa will be reconsidering the prior art and how it may affect the claims. Mr. Celsa also raised some concerns about the scope of the claims. No claim language was specifically discussed.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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